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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,289	05/31/2002	Vega Masignani	PP01639.102; 2300-1639	6882

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,289	MASIGNANI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,9,10,13,15,17,19,21 and 23-33* is/are pending in the application.

4a) Of the above claim(s) *7, 9, 13, 15, 17, 19, 21, 23, 24 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 12/13/06 in response to the non-final Office Action mailed 06/16/06.

Status of Claims

2) Claim 1 has been amended via the amendment filed 12/13/06.

Claims 1, 7, 9, 10, 13, 15, 17, 19, 21 and 23-33 are pending.

Claims 1, 10 and 25-32 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

5) The rejection of claim 1 and those dependent therefrom made in paragraph 9 of the Office Action mailed 06/16/06 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is /withdrawn in light of Applicants' amendment to the base claim.

6) The rejection of claims 1, 10 and 25-32 made in paragraph 10 of the Office Action mailed 06/16/06 under 35 U.S.C. § 112, first paragraph, with regard to the deposit issue, is withdrawn in light of Applicants' amendment to the base claim.

7) The rejection of claims 1, 10 and 25-32 made in paragraph 11 of the Office Action mailed 06/16/06 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the full scope, is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

8) The rejection of claim 1 made in paragraph 12(a) of the Office Action mailed 06/16/06 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of

Applicants' amendment to the claim.

9) The rejection of claims 10 and 25-32 made in paragraph 12(b) of the Office Action mailed 06/16/06 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

New Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

10) Claim 1 and those dependent therefrom, i.e., claims 10 and 25-32 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, includes the new limitations: 'and wherein the polypeptide can detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample'. Applicants state that the amendment is supported by the original claims 1 and 12 and lines 24 and 25 on page 2 of the specification. A review of the specification indicates the following. The preliminary amendment filed 11/08/04 does not contain claim 12. The original claims 1 and 12 from WO 01/04316 (PCT/IB00/01026) filed 01/14/02 are reproduced below:

> 1. A fragment of a protein disclosed in WO99/36544, wherein the fragment comprise at least one antigenic determinant.
>
> 12. The use of the fragment of claim 1, claim 2 or claim 3, the polypeptide of claim 5, the protein of claim 8, the antibody of claim 7, and/or the nucleic acid of claim 9, in the manufacture of (i) a medicament for treating or preventing infection due to Neisserial bacteria (ii) a diagnostic reagent for detecting the presence of Neisserial bacteria or of antibodies raised against Neisserial bacteria and/or (iii) a reagent which can raise antibodies against Neisserial bacteria.

The original claim 12 above does not refer to a purified polypeptide comprising a contiguous amino acid sequence with at least 70% sequence identity to SEQ ID NO: 1331, wherein the polypeptide has a length of 100 amino acids or less and comprises at least one antigenic determinant and wherein 'the polypeptide can detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample'. Lines 24-25 on page 2 of the specification state that the present invention does not include within its scope antibodies which recognize one of 45 complete protein sequences in WO 99/36544. The new limitation 'antibodies raised against

Neisseria meningitidis serogroup B' does not exclude, but includes antibodies that recognize one of 45 complete protein sequences in WO 99/36544. Furthermore, neither 'a sample', 'a contiguous amino acid sequence with at least 70% sequence identity to SEQ ID NO: 1331', nor 'antibodies raised against *Neisseria meningitidis* serogroup B' are supported in these two original claims and at lines 24-25 of page 2 of the specification, as originally filed. Therefore, the limitations in the claim are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed by pointing to specific lines and pages, for the new limitations, or alternatively, remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

11) Claims 1, 10 and 25-32 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a purified polypeptide having a length of 100 amino acids or less comprising the amino acid sequence of SEQ ID NO: 1331, does not reasonably provide enablement for a polypeptide having a length of 100 amino acids or less (i.e., 5, 10, 20, 25, 35, 50, 70 amino acids etc. up to 100) and comprising a contiguous amino acid sequence with at least 70% sequence identity to SEQ ID NO: 1331, wherein the polypeptide comprises at least one antigenic determinant and wherein 'the polypeptide can detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample', as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;

- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims as amended, encompass a purified polypeptide comprising a contiguous amino acid sequence with at least 70% sequence identity to the 18 amino acid-long sequence of SEQ ID NO: 1331, wherein the purified polypeptide has a length of 100 or less, i.e., 5, 10, 20, 25, 40, 50 etc. up to 100, amino acids and comprises at least one antigenic determinant and wherein 'the polypeptide can detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample'. The limitation 'antigenic determinant' encompasses linear and non-linear antigenic determinants. The limitation '*Neisseria meningitidis* serogroup B' encompasses different serotypes, subtypes, and immunotypes of serogroup B *Neisseria meningitidis.* The limitation 'a sample' encompasses a variety of samples including biological samples such as blood, serum, CSF etc. and non-biological samples. The limitation 'antibodies raised against *Neisseria meningitidis* serogroup B' encompasses IgG, IgM, IgA antibodies etc. raised against serotype, subtype, and immunotype of serogroup B *Neisseria meningitidis.* The limitation 'polypeptide .... comprising a contiguous amino acid sequence with at least 70% sequence identity to the sequence of SEQ ID NO: 1331' encompasses purified polypeptides comprising contiguous amino acid sequences with at least 30% non-identity to the sequence of SEQ ID NO: 1331. The specification indicates diagnostic applications. See lines 17-19 of page 3; line 13 of page 4 of the specification; and section 'Immunodiagnostic Assays' on pages 33 and 34 of the specification. The 'antigenic determinant' is described as including a B-cell epitope and a T-cell epitope (see line 7 of page 5 of the specification). The recited polypeptide variant that is 100 amino acids in length or less and having at least 30% non-identity with the amino acid sequence of SEQ ID NO: 1331 is *required* to have the antigenic determinant and wherein 'the polypeptide can detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample'. The diagnostic applications described in the specification indicate that the claimed composition comprising the at least 30% non-identical polypeptide variant is meant for use in diagnosis of *Neisseria meningitidis* serogroup B infections by detecting antibodies to *Neisseria meningitidis* serogroup B in a sample. However, there is *not one single* showing within the instant specification that a polypeptide having a length of 100 amino acids or less

when varied or altered to have at least 30% non-identity to SEQ ID NO: 1331 would retain the ability to detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample'. The ability to detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample requires the polypeptide variant having at least 30% non-identity to SEQ ID NO: 1331 to bind specifically to antibodies raised against *Neisseria meningitidis* serogroup B in a sample. Not a single polypeptide variant species (let alone a representative number of variant species) having a length of 100 amino acids or less and having at least 30% non-identity to SEQ ID NO: 1331 is shown within the instant specification to bind specifically to antibodies raised against *Neisseria meningitidis* serogroup B and detect antibodies raised against *Neisseria meningitidis* serogroup B in a sample. This is important because an epitope or antigenic determinant on an antigen is known to bind to antibodies via a three-dimensional fit. See pages 58 and 59 of Herbert *et al.* (*The Dictionary of Immunology*, Academic Press, 3rd Edition, London, pages 58-59, 1985). This means that the antigenic determinant in Applicants' less than 100 amino acid-long polypeptide variant that has at least 30% non-identity to SEQ ID NO: 1331 has to have the three dimensional configuration in order to bind and detect in a sample antibodies raised against any serotype, subtype, or immunotype of *Neisseria meningitidis* serogroup B. However, the instant specification lacks evidence with regard to this. Therefore, the full scope of the instant claims is not enabled. There is absolutely no showing of a correlation between the primary or tertiary structure of a polypeptide variant having a length of 100 amino acids or less and that is at least 30% structurally non-identical to SEQ ID NO: 1331 and its ability to bind or detect antibodies raised against any serotype, subtype, or immunotype of *Neisseria meningitidis* serogroup B in a sample. There is no showing that the polypeptide variants encompassed within the scope of the claims tolerate modifications and remain antigenic and detect antibodies raised against any serotype, subtype, or immunotype of *Neisseria meningitidis* serogroup B. With this lack of showing, the Office would look into the literature in the relevant art of polypeptide or peptide variants in order perform the required *Wands* analysis.

A review of the state of the art at the time of the invention, particularly with regard to the unpredictability factor as associated with meningococcal proteins documents the following. The art shows that an alteration even in a single amino acid can eliminate or drastically change one or more biologic function(s) of the polypeptide. For instance, McGuinness *et al.* (*Lancet*

337: 514-517, March 1991, already of record) showed that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate (see abstract and page 514). With particular reference to VR1 and VR2 epitopes of class 1 outer membrane protein of *Neisseria meningitidis*, McGuinness *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993, already of record) also taught that "[a] single amino acid change *within an epitope*, or an amino acid deletion *outside an epitope*, were both associated with *loss of subtype specificity* resulting from a change in the predicted conformation at the apex of the loop structure" (see abstract) [Emphasis added]. One of skill in the art can reasonably expect a loss of immunospecificity to '*Neisserial meningitidis* strain B' in Applicants' polypeptide variant which has up to 30% non-identity to the amino acid sequence of SEQ ID NO: 1331. It should be noted that Applicants have neither identified a functional site, i.e., an antigenic determinant that binds or detects antibodies raised against *Neisseria meningitidis* serogroup B in a sample, in any single polypeptide variant that is 70%, 80%, or 90% identical to the amino acid sequence of SEQ ID NO: 1331, for one of skill in the art to avoid or to include mutation(s) or variation(s) within or outside the antigenic determinant. The lack of disclosure and specific guidance within the instant specification combined with the art-recognized functional unpredictability would require one of skill in the art to engage in considerable amount of undue experimentation.

With regard to the structure-function relationship of an amino acid sequence in general, Rudinger *et al.* (*In*: *Peptide Hormones*. (Ed) JA Parsons, University Park Press, June 1976, already of record) taught that 'the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study' (see page 6). Rudinger *et al.* further taught that 'it is impossible to attach a unique significance to any residue in a sequence' and that a 'given amino acid will not by any means have the same significance in different peptide sequences (i.e., fragments), or even in different positions of the same sequence (see page 3). The lack of guidance within the instant specification in combination with Rudinger's teachings supports the Office's position regarding the unpredictability factor and the need to engage in considerable amount of undue experimentation.

The state of the art on microbial polypeptides in general indicates that a random replacement affecting the epitopic amino acid positions that are critical to the three-dimensional conformational structure and specific binding property of a protein, would result in a polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986, already of record) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively **unrecognizable by any of the antibodies** in the polyclonal pool. [Emphasis added].

Thus, it has already been established in the art that variations in critical residues at specific positions of an amino acid sequence could result in a polypeptide variant, which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. There is no predictability that a polypeptide variant having up to 30% sequence non-identity to the native polypeptide of SEQ ID NO: 1331 would remain antigenically immunospecific to *Neisseria meningitidis* serogroup B.

The above-cited references reasonably demonstrate that even a single amino acid substitution/deletion will often dramatically affect the immunospecific biological activity or characteristics of a protein or polypeptide. Clearly, with up to 30% sequence non-identity to the polypeptide of SEQ ID NO: 1331, the *Neisseria meningitidis* serogroup B-specific antigenic function of the claimed polypeptide variant cannot be predicted, merely based on the sequence identity with SEQ ID NO: 1331, nor would it be expected to be nearly the same as that of the polypeptide of SEQ ID NO: 1331. Although a skilled artisan might envision making a number of changes in the reference polypeptide sequence of SEQ ID NO: 1331 in accordance with Applicants' disclosure, it is highly uncertain or unpredictable that the polypeptide variant as claimed would retain 'at least one antigenic determinant' wherein 'the polypeptide can detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample'. If one nucleotide base in the nucleotide sequence that encodes the polypeptide of SEQ ID NO: 1331 is

deleted or inserted at a single position within the coding sequence, all the codons downstream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the varied polypeptide expressed will have little in common structurally or functionally with the native polypeptide of SEQ ID NO: 1331. The polynucleotide homologs or variants isolated solely based on percent identity or homology do not predictably display the functions of the native molecules, absent an independent showing that the variant polynucleotide sequence produces a polypeptide variant that functions as recited. The antigenic or binding functions of a gene product based solely on percent sequence identity is unreliable and unpredictable, absent a supportive showing by production of a representative number of 1 to 30% non-identical polypeptide variant species that have the recited and required antigenic determinant and the ability to detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample. For all the reasons delineated above, making and using of the instantly claimed polypeptide variant having the recited ability to elicit an immune response against '*Neisserial meningitidis* strain B' is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed, due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the neisserial and microbial polypeptide art, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

The Courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the 'novel' aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001)*. Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*). A claim must be enabled over its whole breadth. In this respect, if there are doubts, substantiated by verifiable facts, there is lack of sufficient enablement.

Remarks

12) Claims 1, 10 and 25-32 stand rejected.

13) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted to the Office' Central Rightfax number 571-273-8300 via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week.

15) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2007

S. DEVI, PH.D.
PRIMARY EXAMINER